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■

STANDARDS FOR HUMAN BLOOD, BLOOD PRODUCTS AND BIOLOGICAL PRODUCTS

Source Plasma (Human)

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER F—BIOLOGICS

[Docket No. 75N-0366]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Source Plasma (Human)

The Food and Drug Administration is amending the biologics regulations for the manufacture of Source Plasma (Human) based on two separate proposals published in the FEDERAL REGISTER of May 28, 1974 (39 FR 18614) and July 17, 1974 (39 FR 26161). The amendments are effective May 11, 1976.

A. In the May 28 proposal, the Commissioner of Food and Drugs proposed regulations concerning "Current Good Manufacturing Practice for Blood and Blood Components." Proposed § 606.16 *Plasmapheresis* prescribed requirements for obtaining plasma intended for further manufacture into noninjectable products. Interested persons were given until August 26, 1974, to file written comments with the Hearing Clerk, Food and Drug Administration (FDA), regarding the proposal. Twenty-five letters received in response to this proposal related specifically to plasmapherisis. Many of the comments were substantially the same as, or similar to, those received in response to the July 17 proposal, since both proposals concerned products obtained by plasmapheresis intended for further manufacture into noninjectable products.

B. In the July 17 proposal, the Commissioner proposed to amend the Source Plasma (Human) regulations, §§ 640.60 through 640.70 (21 CFR 640.60 through 640.70) by redefining Source Plasma (Human) to include plasma collected by plasmapheresis intended for use in manufacturing noninjectable products, commonly referred to as "clinical chemistry controls" or "diagnostic reagents." In addition, the Commissioner proposed numerous amendments to clarify and strengthen the existing Source Plasma (Human) regulations in light of FDA inspectional and other regulatory experience. Also proposed was an amendment to § 610.40 (21 CFR 610.40) to impose further limitations on the use of hepatitis reactive blood, plasma, or serum in the manufacture of licensed in vitro diagnostic biological products and to provide similar restrictions on the use of hepatitis reactive material in the manufacturing of unlicensed in vitro diagnostic biological products.

Interested persons were given until August 16, 1974 to file written comments regarding the proposal. Seventeen letters of comment addressed that portion of the proposal regarding Source Plasma (Human). Five letters of comment addressed that portion of the proposal concerning the test for hepatitis B surface antigen. The Commissioner responded to these five comments in the final order concerning the test for hepatitis B surface antigen published in the FEDERAL REGISTER of July 15, 1970 (40 FR 29706).

The Commissioner concludes that it is appropriate in this preamble to respond to comments regarding the section on plasmapheresis in the May 28 proposal, as well as the comments to the July 17 Source Plasma (Human) proposal. Items 1, 3, 9, 11, 14, 17, 19, and 47 reflect substantively similar comments that were received in response to the May 28 and July 17 proposals. Items 4, 10, 18, 21, 22, and 23 reflect comments that were received only in response to the May 28 proposal, and the remaining items reflect comments received only in response to the July 17 proposal. To aid the reader, no references are made to the plasmapheresis section of the May proposal. Rather, all comments refer to the corresponding July proposed regulation. A summary of the comments and the Commissioner's conclusions are as follows:

1. Three comments expressed concern that the proposed regulations would curtail the supply of Source Plasma (Human) intended for further manufacture into noninjectable products from overseas operations and from certain blood banks associated with hospitals or located in remote areas, which are distant from licensed plasmapheresis centers. One of the comments stated that blood banks associated with hospitals only plasmapherese donors occassionally, and therefore will probably not bother to obtain a license.

The Commissioner rejects the suggestion that licensing plasma for manufacture into noninjectable products will seriously reduce its supply since many of the establishments that will be applying for a license for Source Plasma (Human) for use in manufacturing noninjectable products are already licensed for plasma for injectable products. The Commissioner recognizes, however, that specific exemptions to the licensing requirements may be necessary to authorize donations in special circumstances, as for an individual who possesses a rare antibody but is located in an area not reasonably accessible to a licensed Source Plasma (Human) facility. Establishments which have identified and obtained donation agreements from persons whose plasma contains special characteristics must be permitted to continue to plasmapherese in cases where the limited numbers of these donors and the infrequent donations might otherwise discourage the obtaining of this material under federal interstate licensure. Accordingly, § 640.71 redesignated as § 640.75 *Alternate procedures* (21 CFR 640.75) provides for collection and processing procedures that are at variance with the regulations, including the licensing requirements, provided that prior approval is obtained from the Director, Bureau of Biologics.

2. Two comments questioned the legislative authority under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act for FDA to promulgate regulations relating to donor protection and to control plasma intended for chemistry controls. One of the comments further suggested that rulemaking concerning this issue should proceed only after a second notice.

In the FEDERAL REGISTER of August 26, 1972 (37 FR 17419), the Commissioner first announced that all establishments engaged in interstate shipment of human plasma were subject to the licensing provisions of section 351 of the Public Health Service Act and proposed standards for the collection and processing of the licensed product, Source Plasma (Human). The Commissioner concluded that the standards must contain provisions to protect the health of plasma donors to ensure a continued, healthy donor population to serve as a source of plasma. Procedures for donor protection, based upon recommendations of the Advisory Committee of the Division of Medical Sciences, National Academy of Sciences—National Research Council, were incorporated in that original proposal.

The donor protection requirements ultimately adopted by the Commissioner and promulgated as part of the final regulation, published in the FEDERAL REGISTER of July 20, 1973 (38 FR 19362), reflect not only the recommendation of the Advisory Committee but also the views of representatives of the plasma collection and fractionation industries and individual citizens who had commented on the proposal. Indeed, the comments suggested even more stringent requirements than originally proposed, and many were incorporated into the final regulation. The opportunity for comment on the authority of the Commissioner to promulgate regulations relating to donor protection was provided when the standards were first proposed. The proposal to expand the definition of Source Plasma (Human) to include plasma intended for noninjectable products, at issue in this rule making action, did not include any revision in the existing regulations.

Moreover, certain aspects of the donor protection requirements directly affect the safety, purity, and potency of the plasma, such as those provisions concerning donor suitability that are designed to assure that plasma is free of disease-carrying agents. In an indirect but no less important manner, the requirements for donor protection assure, as the Commissioner stated more than 3 years ago, that there will be a continuous and healthy donor population. Finally, the Commissioner believes that it is an inherent obligation of government to assure that where standards are established for products, the public health factors that are integral to the product must be considered and protected. Such action is necessary and proper in the exercise of the underlying authority.

In the preamble of the July 1974 proposal on Source Plasma (Human), the Commissioner reiterated the importance of the doner protection provisions in the plasma licensing scheme. The Commissioner also noted the failure of a number of license applicants to comply with the donor protection provisions of the regulations, particularly when these facilities

were processing plasma for use in noninjectable products only. Inadequate donor protection practices defeat one of the major purposes of the regulations; namely, to protect plasma donors. Since the proposal was published, FDA has inspected numerous plasmapheresis facilities that were collecting plasma for use in noninjectable products and has found that some are not observing recognized requirements of donor protection. In some cases, firms that had failed to receive a license due to their inability to comply with the additional standards continued their operations as before, but redirected their plasma to subsequent use for noninjectable products.

It is apparent that the failure of the Source Plasma (Human) regulations to extend to noninjectable products has created a haven for those plasmapheresis facilities that are unwilling to meet the requirements of donor protection. The Commissioner has concluded that these facts justify a redefinition of Source Plasma (Human) to include all plasmapheresis operations, regardless of the eventual use of the plasma. The continued existence of a double standard of donor protection is unacceptable. The eventual use to which a donor's plasma is put is irrelevant to the application of basic measures to protect the plasma donor from the possibility of exploitation during the donor's participation in the plasmapheresis program.

Application of the Source Plasma (Human) licensure requirements and additional standards to plasma for noninjectable products is consistent with the existing statutory scheme since section 351 of the Public Health Service Act applies to all blood components "applicable to the prevention, treatment, or cure of diseases or injuries of man." Human plasma is a blood component within the meaning of the act, and the uses of clinical chemistry controls, typing sera, diagnostic reagents, and the like, place them clearly within the statutory definition. Clinical chemistry controls and diagnostic reagents are used as standards to calibrate equipment in the diagnosis of disease, or they are used directly in assaying specimens of body fluids taken from patients to determine, for example, the presence of disease or the appropriate remedy. All of the information obtained from the use of the plasma and serum as clinical chemistry controls or as diagnostic reagents is used by licensed physicians to treat patients and to evaluate patient response to treatment. A product is "applicable to the prevention, treatment or cure of diseases or injuries of man" when used for any purpose of diagnosis or as an aid in diagnosis (21 CFR 600.3(j)). Thus, the Commissioner concludes that defining Source Plasma (Human) to include plasma for both injectable and noninjectable products is authorized by section 351 of the Public Health Service Act. The additional standards will apply to all such plasma.

Since the reasons for the Commissioner's decision to apply the licensure requirements of Source Plasma (Human) to plasma obtained by plasmapheresis and used for noninjectable products were set forth fully in the proposal, proper time and procedures for public comment have already been provided and no further notice is necessary, as suggested in one of the comments.

3. Four comments objected to the phrase "assuring the donor's safety and the sterility of the licensed Source Plasma (Human)" appearing in the preamble of the proposal. The comments objected to the implication that Source Plasma (Human) must be sterile. The comments stated that to require sterility would serve no useful purpose because current regulations for the final injectable products prepared from Source Plasma (Human) require product sterility. The comments also asserted that the container for plasma intended for manufacturing into noninjectable products need not be sterile or pyrogen-free as such properties are not essential for such product.

The proposed rules did not propose nor do the regulations require that Source Plasma (Human) itself be sterile. However, plasma should be prepared by a method that maximizes the likelihood of an uncontaminated product, particularly for plasma intended for manufacture into injectable products. The Commissioner agrees that containers for plasma for use in noninjectable products need be neither sterile nor pyrogen-free. Although the comments were directed to a phrase in the preamble of the proposal, they are applicable to certain provisions of § 640.68(a) concerning sterile systems, and the Commissioner is revising that provision to require that the interior surface of only those containers used for Source Plasma (Human) intended for manufacturing into injectable products, and all transfer and administration sets inserted into the blood container shall be sterile, pyrogen-free, nontoxic, and compatible with the contents.

4. One comment suggested that the regulations require tests prior to plasmapheresis to determine the sensitivity of a donor's red blood cells to break down (osmotic fragility) to reduce the risk that the cells will not survive after reinfusion into the donor's body (the cell viability syndrome). In addition, the comment suggested that tests to determine the amount of antihemophilic factor and other coagulation factors should be required to detect any coagulation deficiencies as well as to serve as indirect indicators of freedom from liver deficiencies (hepatitic status) reflected by decreased protein synthesis by the liver.

No data were submitted with the comment nor is the Commissioner aware of any data suggesting that the plasmapheresis procedure subjects donors to physical and physio-chemical stresses requiring testing, as suggested by the comment. However, the Commissioner would welcome submission of data to support the suggested testing. In the absence of such data, the comment is rejected.

5. One comment stated that in proposed § 640.60 the phrase "stabilized against clotting" in the definition of Source Plasma (Human) is unnecessary and should be omitted. Another comment indicated that it is not clear whether the phrase refers to "human blood" or "fluid portion of human blood." This comment noted that in the collection of plasma for manufacturing into some reagents, it is necessary for a clot to form to convert the plasma to serum.

The Commissioner concurs that the phrase "stabilized against clotting" is unnecessary since the regulations under § 640.64 currently provide that the anticoagulant be present in the blood container into which the blood is collected. Accordingly, the phrase is deleted from § 640.60 in the final regulations.

6. The present regulations in § 640.63 (b) require that the donor shall be examined by a licensed physician on the day of the first donation or no more than 1 week before the first donation. However, it has come to the attention of the Commissioner that donors who are receiving immunization injections, e.g., D positive red blood cells, for the production of high titer serum are often injected with the antigen a week or more before the first donation. Consequently, such donors may not receive the physical examination before the first immunization.

The Commissioner concludes that it is in the interest of the health of such donors that the initial medical examination be performed before the injection procedure has begun. Accordingly, the Commissioner is amending § 640.63 in the final regulations to require that (1) the initial medical examination of a donor who is to be immunized must be performed within 1 week before the first immunization injection, and (2) the medical examination for plasmaphereses need not be repeated if the first donation occurs within 21 days after the first injection.

7. One comment suggested that proposed § 640.63(e), which prohibits a donor from being plasmapheresed for 8 weeks if the red blood cells have not been returned, be expanded to include individuals who have given a unit of whole blood. Two other comments suggested that the 8-week waiting period is too restrictive and that plasmapheresis should be permitted whenever the hemoglobin or hematocrit value meets prescribed levels.

The Commissioner agrees that the loss of red blood cells to the donor will have the same effect whether the loss results from the donation of whole blood or from failure to return the red blood cells to a plasmapheresis donor. Accordingly, the same 8-week waiting period required by § 640.3(b) (21 CFR 640.3(b)) should apply to both types of donors, and § 640.63 (e) is amended in the final regulations to prohibit plasmapheresis of a donor who has been a whole blood donor within the 8-week period, unless the donor has been examined by a qualified licensed physician and certified by the physician to be acceptable prior to 8 weeks.

The Commissioner disagrees with the two comments suggesting that plasmapheresis should be permitted after a loss

of red blood cells so long as the donor's hemoglobin or hematocrit value meets prescribed levels, regardless of the elapsed time. The respondents apparently do not consider that such donors may again not receive their red blood cells, in which case they may lose the equivalent of two units of whole blood (1,000 milliliters) within a 48-hour period. Such a loss of whole blood could result in a depletion of iron reserves and may endanger a donor's health. The waiting period is necessary to allow the donor's hematocrit value and iron stores to return to levels which are normal for each donor regardless of whether that donor's hematocrit or hemoglobin value meets the generally acceptable level established by the Source Plasma (Human) regulations. Accordingly, the comments are rejected.

8. One comment recommended that in proposed §§ 640.64 and 640.68 the term "non-pyrogenic" be substituted for the term "pyrogen-free." The comment stated that the term "non-pyrogenic" is more scientifically accurate than "pyrogen-free."

The Commissioner rejects the suggestion that one term is more scientifically accurate than the other since both terms indicate that the tested material does not contain pyrogens as determined by the test method used. In addition, since many existing biologic regulations use the term "pyrogen-free," it is logical and consistent to use the same term throughout the biologics regulations. Accordingly, the comment is rejected.

9. Seven comments objected to the provision in proposed § 640.64(c) that an amendment of the product license must be obtained for use of an anticoagulant solution formula differing from that specified in the regulations, when the plasma is intended for manufacture of a noninjectable product. It was suggested that written approval from the Director, Bureau of Biologics, rather than amendment of the product license, would be sufficient and would save time.

The Commissioner advises that written approval by the Director constitutes an amendment of the product license. The time required for approval depends on the complexity and completeness of submitted information and not on any internal differences in the processing of such requests. Accordingly, the comments are rejected.

10. One comment suggested that in § 640.64(c)(1) the name "Anticoagulant Acid Citrate Dextrose Solution" should be changed to be consistent with that of the U.S. Pharmacopeia XIX, "Anticoagulant Citrate Dextrose Solution."

The Commissioner accepts the comment and § 640.64(c) is amended in the final regulations to adopt the change. For consistency in the biologics regulations, the Commissioner is also amending §§ 640.4(d)(1) and 640.7(a)(1)(i) to reflect this name change. The parenthetical abbreviation "ACD" remains unchanged since it is also the correct abbreviation for the USP name for the anticoagulant.

11. Two comments objected to the reference in proposed § 640.65(b) to both "plasma" and "serum" as the material used in performing the quantitative testing for serum proteins or immunoglobulins. The comment indicated that the test is performed on serum only.

The Commissioner advises that some blood establishments are satisfactorily using plasma for the quantitative test for proteins or immunoglobulins. Accordingly, the comment is rejected. However, the Commissioner is amending § 640.65(b) to specify that protein determinations may be performed on either plasma or serum.

12. One comment objected to the restriction in proposed § 640.65(b)(1) that the quantitative tests for serum proteins or immunoglobulins be conducted by the electrophoresis or immunodiffusion tests only. The comment stated that other acceptable tests, such as quantitative nephelometric measurements, should be permitted.

The Commissioner agrees that any quantitative test for determining serum proteins or immunoglobulins should be permitted, if the test is equivalent to the electrophoresis or immunodiffusion tests. Accordingly, the final regulation is amended in § 640.65(b)(1)(i) to permit use of such tests.

13. One comment questioned the value in proposed § 640.65(b)(1) of the quantitative test for serum proteins or immunoglobulins, which is required to be performed every 4 months. It was suggested that the total serum protein test, which is conducted each time a donor is plasmapheresed, would adequately protect donors if an upper limit were established for an acceptable total serum protein level. However, the comment provided no suggested upper limit or data to support deletion of the periodic quantitative test for serium proteins or immunoglobulins test requirements. Another comment indicated that a quantitative test for serum immunoglobulins is necessary to protect the donor's health, thereby supporting the proposed regulation. The respondent submitted data from clinical studies reflecting that donors with stable total serum protein levels may, nevertheless, have marked variations in their gamma globulin composition.

The Commissioner advises that available data support continued requirement of a quantitative test for serum proteins or immunoglobulins. Accordingly, the comment suggesting elimination of such testing is rejected.

14. Six comments objected to the requirement in proposed § 640.65(b)(1) that the total protein determination be performed by a chemical assay method. It was suggested that determination of total protein by use of a refractometer is as good as, if not better than, the chemical assay method.

The Commissioner recognizes that the total protein determination can be adequately obtained by both a refractometer or the chemical assay method. Accordingly, the requirement that only a chemical assay method be used for the total protein determination is deleted from the final regulations.

15. One comment concerning proposed § 640.65(b)(1) presented data to illustrate that the total protein levels of serum, collected in microhematocrit capillary tubes prior to plasmapheresis, averages 0.4 gram per 100 milliliters more than those levels of serum collected from venous blood following removal of the final unit of blood. For this reason, it was suggested that either the total protein value prescribed in § 640.65(b), which is normally determined on a sample of serum collected after withdrawing the first unit of blood from the donor, be lowered from 6.0 to 5.5 grams per 100 milliliters of serum, or that the total protein value prescribed in § 640.63(c)(5), which is normally determined on a sample of plasma collected before withdrawing a unit of blood, be raised from 6.0 to 6.2 grams per 100 milliliters of serum.

The Commissioner is aware that total protein levels may be slightly higher for plasma samples taken before withdrawing a unit of blood compared with the levels determined for serum samples taken after withdrawing a unit of blood. However, these differences may be due to physiologic factors, such as the rate of movement of albumin from the extravascular to the intravascular spaces, which is not significant in determining acceptability of a donor. Since the data presented provide no information on the reasons for the variation in total protein levels, and in view of the extensive satisfactory experience with donor safety resulting from use of the presently required 6.0 grams minimum level of total serum protein per 100 milliliters of serum the Commissioner finds no reason for revising the regulations as proposed by the comment. Accordingly, the comment is rejected.

16. One comment concerning proposed § 640.65(b)(1) stated that there are occasions when a donor's serum is found to be reactive due to a biologic false-positive result from a nonspecific serologic test for syphilis performed by the plasmapheresis facility. However, the donor's serum may subsequently be found nonreactive by a more specific test performed by a state or local health agency or other laboratory that possesses the equipment and expertise for specific testing for syphilis. The comment noted that such a donor would be unjustly rejected under the present requirements and suggested that provision be made to permit the use of results of a more specific test for syphilis that is performed by a qualified testing facility other than the plasmapheresis center.

The Commissioner agrees that results of a more specific test for syphilis that is performed by a qualified laboratory may be used to determine acceptability of a donor. Accordingly, new paragraph (b)(2)(iii) is added to § 640.65 to provide for plasmapheresis of a donor found serologically reactive by a biologic false-positive test result for syphilis provided that no underlying disorder has caused the reactive result and such information

is documented in the donor's file at the plasmapheresis center.

17. Six comments concerning proposed § 640.65(b)(1) stated that manufacturers of positive control serum used in performing the serologic test for syphilis will be unable to obtain adequate material for production of this necessary control reagent since a donor with a reactive serologic test for syphilis may not be plasmapheresed. Another comment questioned the necessity of excluding reactive donors because the noninfectivity of such plasma when used for manufacturing purposes has been well established.

The Commissioner recognizes the importance of maintaining an adequate supply of source material for preparation of positive control reagents for use in performing the serologic test for syphilis. Since the source material for such control reagents can be obtained only from donors with a reactive serological test for syphilis, the Commissioner agrees with the comment suggesting that provisions should be made in the regulations for collecting plasma from such donors. However, the Commissioner believes that syphilitic persons must not be exploited and that it is the obligation of the FDA to assure that its regulations do not sanction continued illness of any person. The Commissioner is aware that such plasma is noninfectious when used for other manufacturing uses. However, he has concluded that prohibiting use of plasma from a donor with a positive serological test for syphilis, except to obtain control reagents, is a necessary and proper element of donor protection. Accordingly, new paragraph (b)(2)(iv) is added to § 640.65 in the final regulations to permit the plasmapheresis of a donor with a reactive serologic test for syphilis only to obtain plasma to be used for further manufacture into control serum for the serological test for syphilis, provided the plasmapheresis center has documentation in the donor's file that treatment has been initiated for syphilis and that continuance in the plasmapheresis program will not interfere with or jeopardize the treatment. In addition, § 640.70(a)(8) (redesignated from proposed § 640.69(e)) requires appropriate labeling for such plasma, and new § 640.72(a)(5) is added to require that distribution records indicate by number those plasma units found reactive to a serological test for syphilis.

18. One comment suggested that the serological test for syphilis in proposed § 640.65(b)(1) should be conducted at each plasmapheresis session rather than at 4-month intervals, as presently required.

The Commissioner advises that the 4-month test for syphilis is designed primarily to identify the disease in donors and to ensure treatment before a donor is seriously affected. Indeed, many States require referral of such individuals to the State health authorities for treatment. Moreover, since the disease-causing spirochetes are destroyed during processing of the plasma, more frequent testing will not increase assurances of the safety of the final product. The respondent submitted no data nor is the Commissioner aware of any data to support a change in this requirement. Accordingly, the comment is rejected.

19. Three comments concerning proposed § 640.65(b)(2) suggested that a provision be included in the regulations to apply to a situation in which a repeat donor does not appear within the 4-month period, but does appear shortly thereafter. For such a donor a sample of blood could not be collected for the required 4-month tests, and the physician would not have a current serum protein or immunoglobulin test result to review. Consequently, the donor would not be able to be immediately plasmapheresed but rather would have to be processed as a new donor in accordance with § 640.63. The comment suggested that the regulations should permit the plasmapheresis center to collect the 4-month sample and continue plasmapheresis of the donor. The review of the results of the 4-month tests would be made within 21 days, and together with the physician's review of the donor's records, a decision would be made as to whether or not the donor could continue on the program.

The Commissioner recognizes that the plasmapheresis center can only request that the donor return for the 4-month tests and has no control over the reliability of the donor to return for such tests. For this reason, the Commissioner accepts the suggestion that the regulations be amended to permit the plasmapheresis center to collect the sample for the 4-month testing and continue plasmapheresis of a donor who returns shortly after the 4-month period. To protect the donor, the physician on the plasmapheresis center's premises must approve the return of the donor to the plasmapheresis program before plasmapheresis is begun. The Commissioner concludes, however, that a donor from whom the plasmapheresis center is unable to obtain a sample for testing for a period exceeding 6 months must be processed as a new donor before returning to the plasmapheresis program.

Accordingly, new paragraph (b)(1)(ii) and (iii) is added to § 640.65 of the final regulations to provide exceptions to the 4-month testing and record review requirements. The new provision also includes a maximum period of 6 months in which the donor may be absent from the program and then reinstated without being considered as a new donor.

20. Four comments concerning proposed § 640.65(b)(2) questioned the necessity of a tracing of the serum protein electrophoretic pattern if the calculated value of each component is available. The comments indicated that such a requirement would exclude the use of more sophisticated instruments that quantitate serum proteins but do not provide tracings.

The Commissioner concurs with the comments since it is not his intention to prevent the use of new equipment or techniques that produce results at least equivalent to existing permitted equipment or techniques. Accordingly, § 640.65(b)(2)(i) of the final regulations requires that the results of the tests include tracings, if any, of the plasma or serum electrophoresis pattern. Tracings are not required if the instruments used for the tests quantitate the plasma or serum proteins but do not provide tracings.

21. Two comments concerning § 640.65(b)(6) of the regulations indicated that the volume of blood permitted to be withdrawn from a donor is excessive.

In the preamble of the Source Plasma (Human) regulations published in the FEDERAL REGISTER of July 20, 1973 (38 FR 19362), the Commissioner established the volume of blood permitted to be withdrawn from a donor. This level was based upon data available at that time and upon discussions with an advisory committee concerned with safeguards for plasma donors. The respondents submitted no new data, nor is the Commissioner aware of any data, to support a reduction of the volume of blood currently permitted to be withdrawn from a donor. Accordingly, the comments are rejected. However, the Commissioner will propose to reduce the currently permitted volume of blood to be withdrawn from a donor in the event that data become available to support such a proposal.

22. One comment requested clarification of the phrase in § 640.65(b)(6), "at one time."

The Commissioner advises that the phrase refers to the volume of blood collected into a single container.

23. Seven comments objected to the requirement in § 640.66 that immunizing agents must be either licensed or approved by the Director of the Bureau of Biologics.

The Commissioner considers licensure and approval of immunizing agents necessary to assure the safety of the donor and recipient of the immunizing agent. It should be noted that approval of a Source Plasma (Human) license application describing procedures for obtaining and transfusing red blood cells intended for immunization constitutes approval of the red blood cells as immunogens pursuant to § 640.66. Accordingly, the comments are rejected.

24. One comment suggested that reference to "Normal Saline" in proposed § 640.68(a) should be replaced with "Sodium Chloride Injection, USP," the official terminology of the United States Pharmacopeia.

The Commissioner agrees, and the final regulation is so amended.

25. One comment concerning proposed § 640.68(a) requested that an appropriate method for the pyrogenicity testing of administration and transfer sets be included in the regulations.

The Commissioner concludes that it is unnecessary to include such procedures in the regulations governing Source Plasma (Human). Such testing is the responsibility of the manufacturer of the sets and must be performed in compliance with the test procedures prescribed in the U.S. Pharmacopeia.

26. Three comments suggested that the regulations in proposed § 640.69(a)

should permit the pooling of plasma that is from different donors and is intended for manufacture into noninjectable products only after the plasma is removed from the red blood cells and the red blood cell container is sealed.

The Commissioner agrees that the regulations should specify that the pooling of plasma that is from different donors and is intended for manufacture into noninjectable products must be performed in a manner that will eliminate the possibility of cross-contamination of one donor's red blood cells with the plasma of another donor. Accordingly, a new paragraph (a)(2) is added to § 640.69 in the final regulations to provide that plasma from one donor may be pooled with plasma from another donor, provided that the plasma from each donor is first separated from the red blood cells and the red blood cell container is sealed.

27. Seven comments concerning proposed § 640.69(a) suggested that the pooling of plasma from two or more donors should be permitted without requiring prior written approval from the Director of the Bureau of Biologics.

Since the regulations are now revised to permit pooling only under prescribed conditions that assure safety of the donor, provision for prior approval is no longer necessary. Accordingly, this requirement is deleted from § 640.69(a) of the final regulations.

28. Three comments objected to the requirement in proposed § 640.69(b) that Source Plasma (Human) be stored at a temperature below −20° C. It was suggested that the storage temperature appropriate for the final product to be prepared from the plasma should be permitted.

The Commissioner agrees that Source Plasma (Human) intended for manufacture into noninjectable products may be stored at a temperature warmer than −20° C if such temperature is appropriate for the intended final product. Section 640.69(b) is amended accordingly with the provision that such temperatures are included in the license application of the Source Plasma (Human) manufacturer. However, the Commissioner advises that Source Plasma (Human) intended for manufacture into injectable products must be stored at a temperature of −20° C or colder. Such storage temperature is necessary to assure preservation of labile factors, such as antihemophilic factor. In addition, this storage temperature is desirable for minimizing bacterial growth if there is any inadvertent contamination of the plasma during processing.

29. One comment suggested that provisions be made in proposed § 640.69(b) for storage of plasma at −5° C immediately after separation from the red blood cells and transfer to −20° C storage when the plasma is frozen. The comment stated that this procedure would reduce the fluctuations in temperature of the −20° C freezer that result from frequent opening of the door to add plasma to the freezer.

The Commissioner advises that the plasma should be frozen as quickly as possible. Many establishments employ a rapid freezing method of dry ice and alcohol to freeze the plasma initially and then place a number of the quick-frozen plasma units into the −20° C freezer. This method reduces the number of times needed to open the −20° C freezer. The respondent's proposed initial storage of plasma at −5° C will not freeze the plasma as quickly as −20° C storage or the rapid freezing method of dry ice and alcohol. Accordingly, the comment is rejected, and no change is made in the final regulation.

30. Two comments suggested that the requirement in proposed § 640.69(c) that each unit of Source Plasma (Human) intended for manufacturing into injectable products be inspected for thawing before issuing is unnecessary. The comments stated that if continuous monitoring of the freezer indicated that the temperature remained at −20° C or colder, such freezer temperature records would be sufficient evidence that the plasma had remained at the proper temperature.

The Commissioner agrees that continuous monitoring of the freezer temperature provides adequate assurance that the plasma has remained frozen throughout the storage period. Accordingly, § 640.69(c) is amended in the final regulations to exempt manufacturers from the requirement of examining each unit of plasma for evidence of thawing, provided that adequate temperature monitoring is maintained and documented by the appropriate records.

31. To be consistent with the organization and format of other biologic regulations, the Commissioner has redesignated paragraph (e) of § 640.69 as § 640.70 *Labeling;* paragraph (f) of § 640.69 as § 640.71 *Manufacturing responsibility;* paragraph (g) of § 640.69 as § 640.72 *Records;* paragraph (h) of § 640.69 as § 640.73 *Reporting of fatal donor reactions;* § 640.70 *Modifications of Source Plasma (Human)* as § 640.74 *Modifications of Source Plasma (Human);* and § 640.71 Alternate procedures as § 640.75 *Alternate procedures.* These revisions do not alter the substance of the regulations, but serve to divide them into more manageable section headings for easier reference.

32. Six comments suggested that the required label statements "For Reagents Only" and "Caution: For Use in Manufacturing Products Not Intended For Injection" in proposed § 640.69(e)(1) and (5) are duplicative and that one of the statements should be deleted. Five of six comments favored retaining the statement "Caution: For Use In Manufacturing Products Not Intended For Injection" since this would enable manufacturers to use a "strip label" to distinguish between the two uses of the plasma, thus eliminating the expense and multiplicity of labels and reducing the chance of labeling mixups.

The Commissioner agrees that having the two statements is redundant. Inasmuch as Source Plasma (Human) is a product with two distinct uses, the Commissioner believes that information regarding the use of the plasma assumes new importance and should be in a prominent position on the label and should be in large type. For this reason, the Commissioner has determined that Source Plasma (Human) intended for further manufacture into noninjectable products shall bear the statement, which may be in the form of a strip label, "Caution: For Use In Manufacturing Noninjectable Products Only" following the proper name of the product. The statements proposed in § 640.69(e)(1) and (5) are no longer needed. This new required label statement is incorporated into § 640.70(a)(2) of the final regulations.

33. The Commissioner is revising proposed § 640.69(e)(3) (redesignated as § 640.70(a)(5)) to permit the use of the donor number or bleed number or both on the label of each unit of Source Plasma (Human). Inspections of Source Plasma (Human) manufacturing establishments by the FDA have revealed that the bleed number may provide more exact identification of a unit of plasma than the donor number. If a donor gives 4 single units of plasma each week, the same donor number may appear on each unit of plasma. However, a new bleed number is assigned to the plasma from a donor each time the donor is plasmapheresed, and the number may provide a better means of identifying a unit of plasma.

34. One comment requested that proposed § 640.69(e)(3) (redesignated § 640.70(a)(5)) be revised to permit the use of a pool number in lieu of individual donor or bleed numbers on the label of plasma that has been pooled from two or more donors, provided the plasmapheresis center maintains records adequate for tracing the blood product to specific donors.

The Commissioner concurs with this request since the processing records maintained by the Source Plasma (Human) manufacturer provide identification of the individual plasma units comprising the pool. Accordingly, § 640.70(a)(5) of the final regulations is amended to permit the use of a pool member in place of the donor or bleed numbers to identify pooled plasma from two or more donors.

35. One comment concerning proposed § 640.69(e)(4) (redesignated as § 640.70(a)(6)) suggested that plasma that has been pooled from two or more donors be labeled with the pooling date of the plasma rather than the collection date of each unit. The comment also proposed that the records of the Source Plasma (Human) manufacturer be required to indicate the collection date of each unit of plasma.

The Commissioner recognizes that all units of plasma may not be added to the pool on the same date, making it difficult to calculate a pooling date that is used for determining the age of the plasma. To eliminate crowding of the label with collection dates of pooled

plasma from two or more donors, the Commissioner has revised § 640.70(a)(6) of the final regulations to permit use of the collection date of the oldest unit of plasma in the pool to be on the plasma label, regardless of when the plasma was pooled, provided that the pooling records show the collection date of each unit comprising the pool.

36. One comment interpreted proposed § 640.69(e) (redesignated as § 640.70) to require that the label of plasma intended for manufacture into noninjectable products must identify the specific product for which that plasma is intended.

The respondent's interpretation is incorrect. Except for plasma for use in manufacturing the positive control serum for the serologic test for syphilis, the regulations do not require that the labeling of Source Plasma (Human) identify the final product that is to be prepared from the plasma. Rather, the regulations require only that, when applicable, the label state that the plasma is intended for manufacture into a noninjectable final product.

37. The Commissioner is amending proposed § 640.69(f) (redesignated as § 640.71) to reflect the types of facilities with which testing arrangements can be made by a Source Plasma (Human) manufacturer. The amendment concerns clarification of the phrase "Clinical laboratory licensed under section 353 of the Public Health Service Act." In view of the fact that a clinical laboratory does not necessarily need to be licensed under section 353 of the Public Health Service Act to meet prescribed standards, the final regulation is revised to include the wording "a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1967 (42 U.S.C. 263a)." Such clinical laboratories include not only those licensed under section 353 of the Public Health Service Act, but also those having letters of exemption from licensing from the Center for Disease Control. Letters of exemption are given to clinical laboratories accredited by the College of American Pathologists, or permitted by New York State. The regulation is further revised to include the phrase "provided the establishment or clinical laboratory is qualified to perform the assigned test." This phrase is added because a "licensed" or "accredited" laboratory may be capable of performing various categories of test procedures, but may not be qualified to perform the specific assigned test(s).

38. Three comments suggested that proposed § 640.69(f)(4)(ii) (redesignated as § 640.71(d)(2)) be amended to permit inspectors from the Center for Disease Control to inspect off-premises testing procedures and facilities.

The Commissioner advises that such amendment is unnecessary. The Center for Disease Control is the government agency charged with administering the provisions of the Clinical Laboratories Improvement Act of 1967 (42 U.S.C. 263a) and has authority to inspect clinical laboratories that it licenses.

39. Six comments concerning proposed § 640.69(f)(4)(iii) (redesignated as § 640.71(d)(3)) suggested that proficiency testing programs from either the Center for Disease Control or the Bureau of Biologics should be acceptable.

The Commissioner believes that it is the responsibility of the FDA to assure that an establishment is capable of performing testing for compliance with the food and drug regulations. Accordingly, the Commissioner rejects the comment and establishments are required to continue participation in the specially designed proficiency testing programs initiated by the FDA.

40. One comment concerning proposed § 640.69(g) (redesignated as § 640.72) suggested that documentation of proper shipping temperatures for plasma intended for manufacturing into noninjectable products should not be required since, in most instances, the shipping temperature would not affect the final product.

The Commissioner concludes that due to the ordinarily short shipping time required for the product and in view of the nature of the product and its intended use, documentation of shipping temperatures for plasma for noninjectable products is unnecessary. Accordingly, the Commissioner accepts the comment, and § 640.72(a)(1) of the final regulations requires that documentation of shipping temperatures be maintained only for plasma intended for manufacturing into injectable products.

41. One comment concerning proposed § 640.69(g) (redesignated as § 640.72) suggested that the regulations provide examples of shipping techniques that assure compliance with the shipping temperature reqirement. The technique suggested was to freeze the plasma in a slanted position and then ship it in an upright position so that any thawing of plasma can be easily detected by inspection.

The Commissioner believes that there is no need to provide examples of techniques for assuring compliance with shipping temperature requirements because many techniques, including the one suggested, are well known by blood establishments and companies specializing in the delivery of Source Plasma (Human). Accordingly, the comment is rejected, and no change is made in the final regulation.

42. One comment concerning proposed § 640.69(g) (redesignated as § 640.72) inquired whether each negative test result for detection of the hepatitis B surface antigen and the amount or weight of plasma withdrawn from a donor each time must be recorded on the individual donor records. The comment suggested that such information is unnecessary for individual donor records since the same information is recorded and maintained in the area where the testing and weighing are performed.

The Commissioner agrees that this information need not be duplicated. Accordingly, the final regulations are amended in § 640.72(a)(2) to provide that negative test results for the detection of hepatitis B surface antigen and the volume or weight of plasma withdrawn from a donor need not be kept on the individual donor record, provided that such information is maintained elsewhere on the premises of the plasmapheresis center where the donor's plasma is collected.

43. One comment concerning proposed § 640.69(g) (redesignated as § 640.72) asked whether the donor record must include a reaction occurring before the actual plasmapheresing was initiated, such as a donor fainting in the waiting room before being processed or fainting when a sample of blood is withdrawn for a laboratory test.

The Commissioner advises that any donor reaction observed while the donor is on the plasmapheresis premises must be noted in the donor's record, whether it occurred before, during, or after collection of the plasma. In addition, donor reactions reported after the donor has left the premises and attributable to the donor's visit to the center shall be recorded on the donor's record. The Commissioner concludes that such occurrences are a necessary part of the donor's total record to determine the donor's suitability to continue in the program. Accordingly, the final regulations are revised in § 640.72(b) to require that any donor reaction while on the plasmapheresis premises or reported to the plasmapheresis center shall be recorded.

44. One comment concerning proposed § 640.69(g) (redesignated as § 640.72) asked whether a record of donor rejection was necessary for a donor who is obviously intoxicated or a donor who returns to the plasmapheresis center before the required time interval between donations. It was suggested that the regulation be amended to require that a record of donor rejection be maintained only if the donor is rejected after initiation of the processing of the donor.

The Commissioner advises that a record of rejection is necessary for prospective donors. The record may provide valuable information for the blood establishment in evaluating the medical history and suitability of the donor for plasmapheresis. Accordingly, the comment is rejected.

45. One comment concerning proposed § 640.69(h) relating to the reporting of severe adverse reactions (incorporated into new § 640.73) requested further more precise identification of reactions that are considered reportable. Two other comments suggested that the requirement that the Bureau of Biologics be notified immediately by telephone of a severe adverse reaction was impractical due to the time changes between the West and East coasts.

The proposed § 640.69 defined a severe reaction as a clinical response that results in death or life-threatening illness. However, the Commissioner recognizes that many clinical responses, if not properly treated, could aggravate or develop into a life-threatening illness. Consequently, the regulation could be misinterpreted to mean that all clinical responses must be reported. Since the

Commissioner is most concerned about life-threatening responses that result in death, to preclude ambiguity, § 640.73 is amended in the regulations to require that only fatal donor reactions must be reported to the Bureau of Biologics. All other donor reactions must be recorded in the records of the plasmapheresis center as required by § 640.72(d).

The Commissioner accepts the comments suggesting that immediate notification, by telephone, of a fatal reaction is impractical due to the time changes between the East and West coasts. Section 640.73 is amended accordingly.

46. One comment concerning proposed § 640.69(h) (incorporated into new § 640.73) inquired how the proposed regulations would affect foreign establishments and suppliers of Source Plasma (Human).

The Commissioner advises that the regulations are applicable to all establishments, both foreign and domestic, that introduce or market Source Plasma (Human) in the United States.

47. Seven comments concerning proposed § 640.71 (redesignated as § 640.75) suggested that the Source Plasma (Human) manufacturer should not be required to obtain approval for an alternate procedure only at the time of licensing or in the form of an amendment to the Source Plasma (Human) product license. The comments stated that amendment of the product license requires too much time and that written approval from the Director of the Bureau of Biologics should be adequate.

The Commissioner advises that approval by the Director of the Bureau of Biologics of any procedure used in processing a licensed product constitutes an amendment of the product license. The time required for approval depends upon the complexity and completeness of submitted information and not upon the characterizaton of the processing of such requests. Accordingly, the comments are rejected.

48. One comment concerning proposed § 640.71 (redesignated as § 640.75) noted that provisions for an alternate procedure applied only to Source Plasma (Human) intended for manufacturing into noninjectable products. The comment suggested that the provision should also apply to plasma for injectable products, such as plasma from a donor who had recently recovered from herpes zoster. Although certain donors may not meet all the requirements of donor suitability, their plasma may be rare and very valuable in the production of therapeutic agents that cannot be obtained from plasma of another donor.

The Commissioner concurs with the suggestion that alternate procedures should apply to Source Plasma (Human) intended for manufacturing into both injectable and noninjectable products, and § 640.75 is so amended in the final regulations.

49. The Commissioner is adding new § 640.76 to the final regulations to require that Source Plasma (Human) for manufacture into injectable products that has been inadvertently exposed to temperatures warmer than −20° C or −5° C during storage or shipment, respectively, must be relabeled as "Source Plasma (Human) Salvaged" and appropriate records made of the cause of the deviation and the corrections taken by the manufacturer. The new section is added in response to a number of inquiries received by the Bureau of Biologics concerning necessary action when the storage or shipping temperature of plasma intended for manufacturing into injectable products exceeds that specified in the regulations. In addition, a new paragraph (b) is added to § 640.70 to prescribe labeling requirements for such products.

50. The Commissioner is amending § 610.53 (21 CFR 610.53 and § 640.70 (redesignated as § 640.74) to correct the references, as needed, to section numbers that have been redesignated.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262) and under authority delegated to the Commissioner (21 CFR 2.120), Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

A. In Part 610, in § 610.53 by revising the listing for Source Plasma (Human) to read as follows:

§ 610.53 Dating periods for specific products.

* * * * *

Source Human.	Plasma	In lieu of an expiration date, the collection date shall appear on the label as prescribed in § 640.70(a)(6) of this chapter.

* * * * *

B. In Part 640 as follows:

1. In § 640.4 by revising its heading and the heading of paragraph (d)(1) to read as follows:

§ 640.4 Collection of blood.

* * * * *

(d) * * *

(1) *Anticoagulant citrate dextrose solution (ACD).* * * *

2. In § 640.7 by revising paragraph (a)(1)(i) to read as follows:

§ 640.7 Labeling.

* * * * *

(a) * * *

(1) * * *

(i) Either "ACD", or "anticoagulant citrate dextrose solution",

* * * * *

3. By revising § 640.60 to read as follows:

§ 640.60 Source Plasma (Human).

The proper name of the product shall be Source Plasma (Human). The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

4. In § 640.63 by revising paragraph (b) and adding new paragraph (e) to read as follows:

§ 640.63 Suitability of donor.

* * * * *

(b) *Initial medical examinations.* (1) Each donor shall be examined by a qualified licensed physician on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no longer than 1 year.

(2) If a donor is to be immunized for the production of high titer plasma, the initial medical examination shall be performed within no more than 1 week before the first immunization injection. The medical examination for plasmapheresis need not be repeated if the first donation occurs within 21 days after the first injection.

(3) Each donor shall be certified to be in good health by the examining physician. The certification of good health shall be on a form supplied by the licensed establishment and shall indicate that the certification applies to the suitability of the individual to be a plasmapheresis donor and, when applicable, an immunized donor.

* * * * *

(e) *Failure to return red blood cells.* Any donor who has not had the red blood cells returned from a unit of blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks unless the donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8-week period.

5. In § 640.64 by revising the introductory text of paragraph (c) and the heading of paragraph (c)(1) to read as follows:

§ 640.64 Collection of blood for Source Plasma (Human).

* * * * *

(c) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulas shall be used in the indicated volumes, except that a different formula may be used for plasma for manufacture into noninjectable products if prior written approval is obtained from the Director of the Bureau of Biologics at the time of licensing or in the form of an amendment to the Source Plasma (Human) product license.

(1) *Anticoagulant citrate dextrose solution (ACD).* * * *

6. In § 640.65 by revising paragraphs (a) and (b)(1) and (2) to read as follows:

§ 640.65 Plasmapheresis.

(a) *Procedure-general.* The plasmapheresis procedure is a procedure in which, during a single visit to the establishment, blood is removed from a donor, the plasma separated from the formed elements, and at least the red blood cells returned to the donor. This procedure shall be described in detail in the product license application.

(b) * * *

(1) (i) A sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter by a qualified licensed physician or by persons under his supervision and trained in such procedure. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immunodiffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: *Provided,* That no longer than 6 months has elapsed since the last sample was collected, and the physician on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4-month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing as prescribed in paragraph (b) (1) (i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2) (i) The accumulated laboratory data, including tracings, if any, of the plasma or serum protein electrophoresis pattern, the calculated values of each component, and the collection records shall be reviewed by a qualified licensed physician within 21 days after the sample is drawn to determine whether or not the donor may continue in the program. The review shall be signed by the reviewing physician. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per 100 milliliters of samples, the donor shall be removed from the program until these values return to normal.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be nonreactive to a serologic test for syphilis, except as provided in paragraph (b) (2) (iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: *Provided,* That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-positive reaction and indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: *Provided,* That the physician on the premises approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

7. By revising § 640.67 to read as follows:

§ 640.67 Test for hepatitis B surface antigen.

Each unit of Source Plasma (Human) shall be nonreactive to a test for the hepatitis B surface antigen as prescrioed in §§ 610.40 and 610.41 of this chapter, except insofar as permitted in § 610.40(d) (2) and (3) of this chapter.

8. In § 640.68 by revising paragraph (a) to read as follows:

§ 640.68 Processing.

(a) *Sterile system.* All administration and transfer sets inserted into blood containers used for processing Source Plasma (Human) intended for manufacturing into injectable or noninjectable products and all interior surfaces of plasma containers used for processing Source Plasma (Human) intended for manufacturing into injectable products shall be sterile, pyrogen-free, nontoxic, and compatible with the contents under normal conditions of use. Only Sodium Chloride Injection USP shall be used as a red blood cell diluent. If the method of separation of the pasma intended for injectable products involves a system in which an airway must be inserted into the plasma container, the airway shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

* * * * *

9. In § 640.69 by revising paragraphs (a), (b), and (c) and deleting paragraphs (e), (f), and (g), as follows:

§ 640.69 General requirements.

(a) *Pooling.* Two units of Source Plasma (Human) from the same donor may be pooled if such units are collected during one plasmapheresis procedure: *Provided,* That the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, for plasma intended for injectable products, gives maximum assurance of a sterile container of plasma.

(1) The pooling of plasma from two or more donors is not permitted in the manufacture of Source Plasma (Human) intended for manufacturing into injectable products.

(2) The pooling of plasma from two or more donors by the manufacturer of Source Plasma (Human) intended for manufacturing into noninjectable products is permitted: *Provided,* That the plasma from two or more donors is pooled after the plasma has been removed from the red blood cells, and after the red blood cell containers are sealed.

(b) *Storage.* Immediately after filling, plasma intended for manufacturing into injectable products shall be stored at a temperature not warmer than 20° C., except for plasma collected as provided in § 640.74. Plasma intended for manufacturing into noninjectable products may be stored at temperatures appropriate for the intended use of the final product, provided these temperatures are included in the Source Plasma (Human) license application.

(c) *Inspection.* Source Plasma (Human) intended for manufacturing into injectable products shall be inspected for evidence of thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at −20° C or colder. If there is evidence that the storage temperature has not been maintained at −20° C or colder, the plasma may be relabeled and issued as provided in § 640.76(a).

* * * * *

(e)–(g) [Removed]

10. By redesignating present § 640.70 *Modification of Source Plasma (Human)* as § 640.74 and adding new § 640.70 to read as follows:

§ 640.70 Labeling.

(a) In addition to the labeling requirements of § 610.62 of this chapter, and in lieu of the requirements in §§ 610.60 and 610.61 of this chapter, the following information shall appear on the label affixed to each container of Source Plasma (Human):

(1) The proper name of the product.

(2) The statement "Caution: For Manufacturing Use Only" for products intended for further manufacturing into injectable products, or the statement, "Caution: For Use In Manufacturing Noninjectable Products Only", for products intended for further manufacturing into noninjectable products. The statement shall follow the proper name in the same size and type of print as the proper name.

(3) The statement "Store at −20° C. or colder": *Provided,* That where plasma is intended for manufacturing into noninjectable products, this statement may be omitted if replaced by a statement of the temperature appropriate for the final product to be prepared from the plasma.

(4) The total volume or weight of plasma and total quantity and type of anticoagulant used.

(5) The donor number or individual bleed number, or both. If plasma is pooled from two or more donors, either all donor numbers, all bleed numbers, or a pool number that is traceable to each individual unit comprising the pool.

(6) The collection date of the plasma. If plasma intended for manufacturing into noninjectable products is pooled from two or more donors, either the collection date for each donation or the collection date of the oldest unit in the pool: *Provided,* That the pooling records show

the collection date for each unit comprising the pool.

(7) A statement as to whether the plasma was collected from normal donors or from immunized donors. In the case of immunized donors, the label shall state the immunizing antigen.

(8) The test for hepatitis B surface antigen used and the results.

(9) When plasma collected from a donor is reactive for the serologic test for syphilis, a statement that the plasma is reactive and must be used only for the manufacturing of positive control reagents for the serologic test for syphillis.

(10) Name, address, and license number of the manufacturer.

(b) Source Plasma (Human) diverted for Source Plasma (Human) Salvaged shall be relabeled "Source Plasma (Human) Salvaged" as prescribed in § 640.76. Immediately following the proper name of the product, the labeling shall conspicuously state "CAUTION: DO NOT USE FOR PRODUCTS REQUIRING LABILE FACTORS" and, where applicable, "STORAGE TEMPERATURE EXCEEDED −20° C." or "SHIPPING TEMPERATURE EXCEEDED −5° C."

11. By adding new § 640.71 to read as follows:

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacture of Source Plasma (Human), including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma (Human), except that the following tests may be performed by personnel of an establishment licensed for blood or blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a): *Provided*, The establishment or the clinical laboratory is qualified to perform the assigned test(s).

(1) The test for hepatitis B surface antigen.

(2) The total plasma or serum protein and the quantitative test for plasma or serum proteins or for immunoglobulins.

(3) The serologic test for syphilis.

(b) Such testing shall not be considered divided manufacturing, which requires two product licenses for Source Plasma (Human): *Provided*, That

(1) The results of such tests are maintained by the establishment licensed for Source Plasma (Human) whereby such results may be reviewed by a licensed physician as required in § 640.65(b)(2) and by an authorized representative of the Food and Drug Administration.

(2) The Source Plasma (Human) manufacturer has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Bureau of Biologics, Food and Drug Administration.

12. By adding new § 640.72 to read as follows:

§ 640.72 Records.

(a) In addition to the recordkeeping requirements of this subchapter, the following records shall be maintained:

(1) Documentation compiled every 3 months establishing that the shipping temperature requirements of § 600.15 of this title and § 640.74(b)(2) are being met for Source Plasma (Human) intended for manufacture into injectable products.

(2) For each donor, a separate and complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., undertaken pursuant to §§ 640.63, 640.65, 640.66 and 640.67, except that negative test results for the detection of the hepatitis B surface antigen and the volume or weight of plasma withdrawn from a donor need not be kept on the individual donor record: *Provided*, That such information is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

(3) The original or a clear copy of the donor's written consent for participation in the plasmapheresis program or for immunization.

(4) The certification of the donor's good health as prescribed in § 640.63(b)(3).

(5) If plasma that is reactive to a serologic test for syphilis is issued as prescribed in § 640.65(b)(2)(iv), the distribution records shall indicate by number those units that are reactive.

(b) Each donor record must be directly cross-referenced to the unit(s) of Source Plasma (Human) associated with the donor.

(c) If a repeat donor is rejected or a donor's plasma is found unsuitable, the donor's record shall contain a full explanation for the rejection.

(d) If a donor has a reaction while on the plasmapheresis premises, or a donor reaction is reported to the center after the donor has left the premises, the donor's record shall contain a full explanation of the reaction, including the measures taken to assist the donor and the outcome of the incident.

13. By adding new § 640.73 to read as follows:

§ 640.73 Reporting of fatal donor reactions.

If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis the Director of the Bureau of Biologics shall be notified by telephone as soon as possible. If the facility is located outside of the continental United States, notification by cable or telegram shall be acceptable.

14. By amending redesignated § 640.74 (formerly § 640.70) by revising paragraph (b)(4) to read as follows:

§ 640.74 Modification of Source Plasma (Human).

* * * * *

(b) * * *

(4) The label affixed to each container of liquid Source Plasma (Human) shall contain, in addition to the information required by § 640.70(a) but excluding § 640.70(a)(3), the name of the manufacturer of the final blood derivative product for whom it was prepared.

* * * * *

15. By adding new §§ 640.75 and 640.76 to read as follows:

§ 640.75 Alternate procedures.

Source Plasma (Human) may be collected and processed at variance with one or more of the requirements of this subpart, including the licensing requirements: *Provided*, That prior approval for such alternate procedures is obtained from the Director of the Bureau of Biologics. Such approval may be obtained orally but must be followed by a written request and a written approval.

§ 640.76 Products stored or shipped at unacceptable temperatures.

(a) Source Plasma (Human) intended for manufacture into injectable products that is inadvertently exposed to a storage temperature warmer than −20° C and colder than 10° C may be issued only if labeled as "Source Plasma (Human) Salvaged". The label shall be revised before issuance and appropriate records shall be maintained identifying the units involved, their disposition, and fully explaining the conditions that caused the temperature exposure.

(b) Source Plasma (Human) for manufacture into injectable products that is inadvertently exposed to shipping temperatures warmer than −5° C and colder than 10° C shall be labeled by the plasma derivative manufacturer as "Source Plasma (Human) Salvaged". Appropriate records shall be maintained identifying the units involved, their disposition, and fully explaining the conditions that caused the accidental temperature exposure.

(c) Source Plasma (Human) shall be relabeled as "Source Plasma (Human) Salvaged" by covering the original label with either (1) a complete new label containing the appropriate information or (2) a partial label affixed to the original label and containing the appropriate new information, which covers the incorrect information regarding storage temperature.

Effective date. This regulation shall be effective on May 11, 1976.

Plasmaphereses establishments that have not previously submitted license ap-

plications because they were producing source plasma intended for noninjectable use only shall file an establishment and product license application by May 11, 1976.

Plasmaphereses establishments that have pending or approved license applications for Source Plasma (Human) intended for injectable products shall file appropriate amendments by May 11, 1976.

Until such time as final action has been taken regarding approval or denial of a seemingly valid license application or amendment, establishments may continue to ship Source Plasma (Human): *Provided*, That these additional standards for Source Plasma (Human) are being adhered to in all respects.

(Sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262))

Dated: March 4, 1976.

SAM D. FINE,
Associate Commissioner for Compliance.

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